1 Introduction

Humans naturally exhale hundreds of organic compounds that not only represent the physiological condition according to their presence and quantity but are also influenced by diet and potential disease metabolites. Within the entire world of living specimens, the recognition of odors is an essential pathway for transmitting information, which may range from the presence of potential predators to the transmission of information between individual organisms. Taking advantage of the specificity of information from the odors within exhaled breath (EB) dates back to the very beginning of medical practices. Later, during his pioneering analysis elucidating the composition of exhaled air, Pauling[1] particularly emphasized the importance of recognizing selected biomarkers as indicators in clinical/medical diagnostics. Since then, a plethora of reports have aimed at correlating biomarkers present within the EB matrix to physiological conditions, diseases, and/or infections (Fig. 1). Despite the fact that the presence, origin, and physiological relevance of many components in breath are not yet fully understood, the composition of EB—and likewise, exhaled breath condensate (EBC)—reflects the biochemical processes and their "metabolic results" occurring within the body and may ideally be correlated to the physiological status, the progression of a disease, and the therapeutic progress/clinical treatment of patients. Given the noninvasiveness of the sampling procedure and the associated comfort for the patient, it is immediately evident that understanding the molecular profile of EB and its variations resulting from certain types of diseases provides a unique diagnostic window.

Although the olfactory analysis of breath can be traced back to ancient times, it is the recent trend toward point-of-care (POC) diagnostics that has revived interest in exhaled breath analysis (EBA) and, in particular, compact diagnostic and/or sensing technologies. Hence, the molecular fingerprint of EB has significant potential in clinical diagnosis, especially for early disease detection and personalized clinical treatment, which is nowadays promoted as personalized medicine.[2] Next to lung cancer and breast cancer, various lung diseases include asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome, and pneumonia, but schizophrenia and diabetes are pathophysiological conditions of interest. Although there is no global definition of which and how many biomarkers in the exhaled air are required for identifying, classifying, and distinguishing among various types of diseases, these biomarker profiles are reproducibly present in the EB matrix. In seminal studies, it has been shown that only by the smell of the EB of patients, dogs are, for example, capable of discriminating between healthy patients and patients with lung cancer[3,4] (Table 1). These data corroborate the hypothesis that there is a repeatedly recognizable and distinct change in the molecular composition of the EB profile, and that this odor change in disease patients is

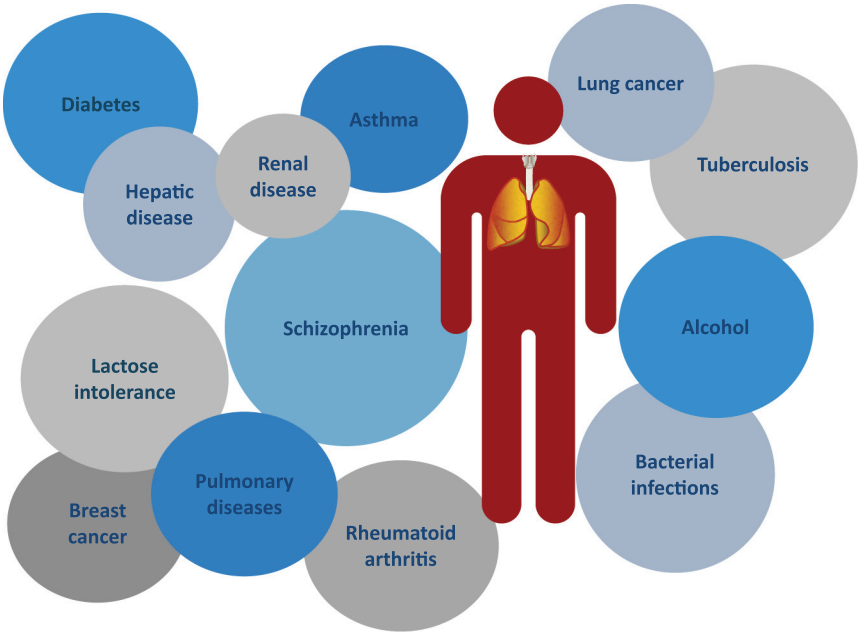

Figure 1 Examples of diseases that can be identified via EBA.

Table 1 Historical milestones in EBA.

Date	Remark	Reference
—	Hippocrates: established the relation of breath aroma and disease	5
Around 1550	Paracelsus: disease reflects in bad breath	
1784	Lavoisier: discovered that EB contains carbon dioxide	6
1800	Nebelthau: determination of acetone in EB	7
1874	Anstie: determination of ethanol in breath	8
1970	Pauling: first analysis of breath via GC with >100 volatile organic compounds identified	1
Today	>3000 volatile organic compounds identified in EB	9

presumably related to changes in the composition and concentration levels of panels of volatile constituents versus healthy subjects.

Although EBA techniques provide a promising diagnostic platform, they are not yet routinely applied at hospitals and clinics—and even less so at the physician's office. This trend may be attributed to the fact that conventional EBA utilizes analytical methods based predominantly on chromatographic techniques,

including gas chromatography (GC) and liquid chromatography (LC), coupled to molecularly selective detection schemes such as mass spectrometry (MS). The cost of instrumentation, supplies, maintenance, and trained personnel for operation is usually prohibitive for screening in a physician's office and limits more widespread application in hospitals and clinics, with the possible exception of intensive care scenarios.

The optical sensing schemes for EBA discussed here offer potential solutions because they are compact, low cost, and portable, but they first need to overcome the usual entry barriers of the medical market. In addition, most sensing technologies have not yet reached the technical maturity required for clinical applications. Yet, without doubt the interdisciplinary collaboration between technology developers in chemistry, physics, materials science, and the engineering disciplines with end users, i.e., clinicians, medical doctors, and physicians, will facilitate establishing EBA based on advanced sensor technologies as a commercially competitive approach that is complementary to conventional analytical techniques with similar or superior performance.

Initiated by recent developments in personalized medicine, analysis of the EB matrix via sensing technologies may not only allow identifying a wide variety of compounds in EB complementary to conventional diagnostics but also monitoring disease states and treatment progress on a routine basis. While nowadays breath diagnostics have already been used to diagnose and monitor asthma, lung cancer, transplant organ rejection, and others,[5] breath analysis is still frequently referred to as a methodology still in its infancy. However, with the emergence of appropriate sensor technologies, potential advantages versus conventional clinical analysis include noninvasiveness, low(er) cost, and—at least in some scenarios—real-time or close to real-time analysis.

2 State of the Art and Challenges

EB is composed of a highly complex molecular matrix, which contains both abundant species such as nitrogen, oxygen, water, and carbon dioxide, as well as trace constituents comprising nearly 3500 volatile organic compounds (VOCs) at extremely low concentration levels (i.e., nanomolar to picomolar; 10^{-9} to 10^{-12} mol L^{-1}). Within this molecular fingerprint, it is estimated that ~50% of the identified VOCs are of endogenous origin. Given that ~200 to 300 VOCs are commonly detected in breath samples, the analytical challenges in dealing with a molecularly disperse and complex matrix of high variability at trace-to-ultratrace concentration levels are immediately evident. Next to the concentration variations, breath constituents also widely vary in molecular weight and activity/reactivity/functionality considering—just to name a few of the more prevalent VOCs—e.g., isoprene, ammonia, acetone, methane, or carbon monoxide (Fig. 2). An additional level of complexity results from the fact that abundant components are by far present at constant levels or within rather well-defined